D/ 7511 / LINURON 1-12-87

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

RELEASABLE

JAN 12 1987

MEMORANDUM

SUBJECT: Dupont rebuttal comments on PD-1, linuron dietary and exposure risk assessment; Caswell 528; EPA I.D. # 035506; Project 7-0149; Record No. 184,982

TO: Michael McDavit, Review Manager
Special Review Branch (TS-767C)
and
Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: James N. Rowe, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division/HED (TS-769C)
James N. Rowe 1/8/87

THRU: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V
Toxicology Branch/HED (TS-769C)
1/8/87
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch/HED (TS-769C)
1/10/87

ACTION: Review of Dupont rebuttal comments entitled, "Linuron- Dietary Exposure and Risk, Response to Special Review/Reregistration Guidance Document- EPA Case No. 47 (6/29/84)" dated October 3, 1986; Caswell 528; EPA I.D. # 035506; Project 7-0149; Record No. 184,982

DISCUSSION/RECOMMENDATIONS: Dupont has submitted data in which the oncogenic risk of dietary exposure to linuron has been recalculated 1) using new residue data on soybeans, 2) dropping the crops wheat, oats, barley and rye (zero percent used) and 3) with a new Q* developed from different statistical modelling techniques. Toxicology Branch will not address the issue of residue data but defers to RCB on this issue. However, it is the reviewer's understanding (personal communication from J. Garbus, RCB) that RCB does not consider the residue data in this submission acceptable due to considerable deficiencies in the experimental design of the trials, inadequate descriptions of sample histories and of analytical methodology and a total lack of raw sample and validation data.

The Toxicology Biostatistics Team was requested to evaluate the rebuttal comments submitted by Dupont with regard to the appropriateness of the statistical models employed in their risk estimates (see Attachment). Several conclusions from that review are noted:

° The issue of fitness of the mathematical model to rodent tumor rates is not considered germane by the EPA to risk extrapolations at low-dose exposures unless the Agency accepts the registrants claim as to the mechanism of action. The Agency has selected the multi-stage model approach as having the most biological validity.

° The virtually safe dose level alluded to by the registrant is not germane to the OPP mission since the Office of Pesticide Programs uses an upper bound on risk estimated for specific environmental exposures associated with use of the chemical for expected residues in the diet or tolerances for dietary components.

° The EPA does not agree with the registrant that there is no apparent evidence of a dose-response relationship for hyperplasia (p. 32 of Dupont report). The addition of hyperplasias to the adenomatous animals smoothes out the dose-response relationship and a highly significant ($p<0.01$) dose-reponse slope (Cochran-Armitage test) is observed for animals with hyperplasia and/or adenomas.

Based on the comments reviewed above, the earlier EPA risk assessment is concluded to be appropriate and no changes in the findings of the risk assessment are recommended at this time. The issue of the mechanism of action of linuron (i.e., mediated through a pituitary-testes hormonal feedback mechanism) has been reviewed in a separate D.E.R. (memo from J. Rowe to M. McDavitt, dated 1/6/87 re: Project No. 7-0134, Record No. 183738). The data in that submission were suggestive but not definitive of a secondary hormonal mechanism for linurons' oncogenicity. The reviewer will request that this issue be considered by the Toxicology Branch Peer Review Committee.

ATTACHMENT

cc K. Barbehenn (TS-769C)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

DEC 31 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Linuron Special Review Comments on Risk Assessment

FROM: Bertram D. Litt, Leader, Biostatistics Team
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769)

12/31/86

TO: Mike McDavitt
Special Review Branch/RD (TS-767)

and

James N. Rowe, Ph.D.
Section V, Toxicology Branch/HED (TS-769)

THRU: Reto Engler, Chief
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769)

Several substantive issues need to be resolved before the appropriate quantitative risk assessment procedures can be applied. As these issues are not yet resolved, it has been necessary to consider what changes, if any, need to be made to earlier EPA estimates based on two sets of assumptions. No comment is made below with reference to dietary risks as this step is accomplished by multiplying the dietary exposure estimate by the cancer potency estimate. Thus the problems for resolution are: a) determining the Linuron exposure associated with various individual food substances or raw agricultural commodities; b) determination of the cancer potency estimates. If the Agency accepts the registrants claim as to mechanism of action it may be reasonable to select the best fitting model. Otherwise, the issue of fitness of a mathematical model to rodent tumor rates observed in a standard two year feeding study or cancer study is not considered by EPA to be germane to the downward extrapolation of the observed values (to the region of low-dose exposure expected in human residues). It has been frequently shown that most to of the standard approaches to mathematical modeling fit positve cancer bioassay data similarly in that none may reject the null hypotnesis of lack of fit at $p < .05$. However, it is not possible to obtain a cost-effective cancer bioassay at the dose levels of interest, i.e., rates $\leq .001$ or 1/1,000, as the required sample size per dose level is prohibitive. The EPA

has therefore selected the multi-stage model approach to cancer and tumor induction as having the most biological validity in the absence of data which illustrate the mechanism of action for the subject chemical in inducing and/or promoting cancer. Thus the EPA estimates of cancer potency should be used if the mechanism of action arguments submitted by the registrant are rejected. Conversely the registrants figures should be accepted if the EPA is prepared to accept the registrants arguments as being scientifically valid.

Secondly, the virtually safe dose level of a chemical alluded to by the registrant also not germane to the OPP mission. The concept of a virturally safe dose for estimating a minimum concentration of the chemical which assures that tne additional risk of cancer associated with that level of lifetime exposure to the subject chemical will not exceed some very low rate such as 1 per million (10^{-6}) or 1 per hundred million (10^{-8}) is the concern addressed by EPA when safe concentration is water on air are evaluated. But, in the Office of Pesticide Products upper bounds on risk are estimated for specific environmental exposures associated with use of the chemical for expected residues in or tolerances for dietary components.

Thirdly the company analysis of hyperplasia is not in agreement with our findings. The data in Table 2 of attachment 3 to the October 3, 1986 "Response to Special Review ..." is misleading in Table A below we show the DuPont figures and in Table B we show the additional tabulations needed to assess the additive effects of Linuron on the test histology:

TABLE A

	Hyperplasia			Adenoma	
	Event	Evaluable	Rate	Events	Rate
Control	1	68	.0147	4	.0588
50 ppm	5	56	.0893	9	.1607
150 ppm	4	64	.0625	19	.2969
625 ppm	6	66	.0909	37	.5606

4

TABLE B

	Hyperplasia in Animals Free of Adenomas			Hyperplasia and/or Adenoma		
	Event	Evaluable	Rate	Events	Evaluable	Rate
Control	1	64	.0156	5	68	.0735
50 ppm	5	47	.1064	14	56	.2500
150 ppm	2	45	.0444	21	64	.3282
625 ppm	6	29	.2069	43	66	.6515

If hyperplasia contributed no additional information one would expect little gain either by looking at the total event rate or from the subgroup who do not have more advanced disease. Adding the hyperplasias to the adenomatous animals has smoothed out the dose-response relationship and a highly significant, $p < .01$, dose response slope (Cochran-Armitage test) is observed for animals with hyperplasia but not more advanced disease.

We conclude tnat if the data are assumed to behave according to multistage cancer theory, the earlier EPA risk assessments are appropriate. If, however, the du Pont presentation on mechanism of action is acceptable, then their approach is acceptable.

#15 12/31/86 sp

5